AD_____

Award Number: DAMD17-98-1-8180

TITLE: Impact of Breast Cancer Treatments on Gonadal Function and Reproductive Health

PRINCIPAL INVESTIGATOR: Patricia A. Ganz, M.D.

CONTRACTING ORGANIZATION: University of California
Los Angeles, California 90095-1406

REPORT DATE: October 2003

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	September 2003	Annual Summaary(1 Sep 2000 - 31 Aug 2003)

4. TITLE AND SUBTITLE
Impact of Breast Cancer Treatments on Gonadal Function and Reproductive Health

5. FUNDING NUMBERS
DAMD17-98-1-8180

6. AUTHOR(S)
Patricia A. Ganz, M.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of California
Los Angeles, CA 90095-1406

E-Mail: pganz@ucla.edu

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 Words)

This fifth and final year has been spent analyzing data and reporting on the multiple phases of the Cancer and Menopause Study (CAMS). The main results paper on the baseline CAMS data, "Breast Cancer in Younger Women: Reproductive and Late Health Effects of Treatment," was completed and accepted for publication by the Journal of Clinical Oncology. Two additional papers have been submitted to peer-reviewed journals for consideration, and a third has been accepted for publication. These papers include analyses on the relationship between cancer survivors' treatment experience and quality of life with 1) physical activity, 2) menopausal transition and symptoms and 3) cognitive function. Additional analyses are currently underway to examine more CAMS data, including investigation of bone density, fatigue, use of complementary and alternative medicines, biologic markers and body composition data, and their relationship to various facets of the cancer survivor experience.

14. SUBJECT TERMS
Breast Cancer, Menopause, Reproductive Health, Osteoporosis, Cardiac Risk Factors, Cognitive Function

15. NUMBER OF PAGES
27

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

FOREWORD

Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the U.S. Army.

N/A Where copyrighted material is quoted, permission has been obtained to use such material.

N/A Where material from documents designated for limited distribution is quoted, permission has been obtained to use the material.

N/A Citations of commercial organizations and trade names in this report do not constitute an official Department of Army endorsement or approval of the products or services of these organizations.

N/A In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and use of Laboratory Animals of the Institute of Laboratory Resources, national Research Council (NIH Publication No. 86-23, Revised 1985).

X For the protection of human subjects, the investigator(s) adhered to policies of applicable Federal Law 45 CFR 46.

N/A In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

N/A In the conduct of research utilizing recombinant DNA, the investigator(s) adhered to the NIH Guidelines for Research Involving Recombinant DNA Molecules.

N/A In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.

Patricia Gary 10/21/03

PI - Signature Date

TABLE OF CONTENTS

Introduction

There is a growing body of epidemiological literature supporting the positive relationship between a woman's endogenous lifetime hormone exposure and the risk of breast cancer[1-3]. Specifically, early menarche and late menopause are associated with increased risk of breast cancer, and this risk is reduced by surgical oophorectomy in the premenopause. Breast cancer adjuvant treatments often lead to premature menopause, and this may be an important factor in the efficacy of these treatments in younger women[4,5]. However, women who experience premature menopause are at increased risk of earlier cardiovascular disease, as well as premature osteoporosis. There is uncertainty about how all of these factors play out in breast cancer survivors who have experienced premenopausal breast cancer, and may become prematurely menopausal as a result of their treatment. Therefore, the primary focus of this cross-sectional study is to examine gonadal function and reproductive health comprehensively in long-term survivors of breast cancer.

Specific Aims

1. To recruit a sample of breast cancer survivors (BCS) who were 50 years or younger at diagnosis, and were treated initially at the Jonsson Comprehensive Cancer Center at UCLA between 1994 and 1997, to complement a prior study of similar women treated between 1989 and 1994. (Phase One)

2. To recruit additional subjects with identical characteristics treated at Kaiser Permanente West Los Angeles or Kaiser Permanente Sunset between 1989 and 1997. (Phase One)

3. To survey these BCS to determine the effects of past treatment on menstrual history patterns and fertility, as well as past and current menopausal symptoms, and current health-related quality of life. (Phase One)

4. To measure current reproductive hormone status, cardiovascular lipid profiles, body composition and bone mineral density (BMD) in these BCS to assess the late effects of breast cancer treatment on risk factors for coronary artery disease and osteoporotic fractures. (Phase Two)

5. To measure neurocognitive functioning in these BCS to examine whether a relationship exists between various domains of cognitive functioning and type of adjuvant therapy received. (Phase Three)

6. To measure longitudinal BMD in these BCS, 18 months after the initial BMD in Phase Two, to examine if group differences exist among women who received different types of adjuvant therapy. (Phase Four)

Description of Phases 1, 2, 3, and 4

The study was conducted in four phases. In phase one, the UCLA Medical Center Tumor Registry and the Kaiser Permanente Tumor Registry were used to identify a group of breast cancer survivors who were 50 years or younger at the time of diagnosis and who were disease free at the time of recruitment. Eligible breast cancer survivors (BCS) were invited to participate in the study and were asked to complete a survey questionnaire that reviewed their menstrual and reproductive history, medication history (including past and current use of contraceptive and non-contraceptive hormones), pregnancy/fertility history, past and current symptoms that may be menopause related, use of alternative therapies, diet and physical activity levels, as well as standardized measures of health-related quality of life. The survey also asked detailed information about each subject's cancer treatment, including type and duration of chemotherapy and hormone therapy received. In addition to analyzing the results from the survey, we examined the medical and demographic characteristics of breast cancer survivors who participated in comparison with those who refused.

In phase two of the research, all BCS who completed the phase one survey questionnaire and who lived in California were invited to come to UCLA for an in-person visit to complete physical and laboratory studies. These included blood work for evaluation of cardiovascular lipids and gonadal hormones; measurement of blood pressure, height, weight and waist/hip girth, and performance of a bone mineral density test (BMD). The results of the questionnaire data and medical treatment details from phase one, as well as current gonadal hormone levels, will be used to explore the predictors of current health status/health-related quality of life, cardiovascular lipids, and bone mineral density. The analyses planned will examine whether a relationship exists between menstrual patterns after breast cancer and current health-related quality of life, lipid profiles, bone mineral density or body composition. These data will be useful in the management of women who are currently long-term survivors of breast cancer, and can be used to provide supporting pilot data for the design of a prospective longitudinal study examining the impact of breast cancer treatment on the long-term reproductive health of premenopausal women with breast cancer. Some of these analyses are completed and others are still ongoing.

Since our original study was designed, we added two additional components - a study of neurocognitive functioning (phase three), and a longitudinal follow-up study of bone density (phase four). In phase three of the research, women between 2 and 5 years post-diagnosis who completed phases one and two and who met other eligibility criteria were invited to come to UCLA for an in-person visit to complete a battery of neurocognitive functioning tests. In addition to the neurocognitive tests, we collected saliva samples for cortisol, performed a single blood draw for immune function studies, as well as measured blood pressure and heart rate. We eventually discontinued collecting saliva samples, because 1) a preliminary analysis of cortisol levels during and after testing showed no stress effect, and 2) by eliminating saliva collection, we were able to reduce the appointment time from four hours to 2.5 hours, thus reducing subject burden. We also invited women with no history of breast cancer to participate as control subjects

for this phase of the study. The main analysis examined whether there was a relationship between cognitive functioning and type of adjuvant therapy received (chemotherapy alone; both chemotherapy and tamoxifen; or no therapy). We also compared neurocognitive functioning between breast cancer survivors and women with no history of breast cancer. The blood measurement was for examination of immune functioning.

In phase four of the research, women who completed phase two were invited back to receive a follow-up bone mineral density at 18 months after the initial bone density study. We added this phase to examine whether observed differences from the cross-sectional evaluation persisted over time. We plan to compare group data between the initial and the follow-up BMDs.

Final Report for the Period October 1, 1998 through September 30, 2003

During the course of the five years covered by this final report, a wealth of information was collected on the long-term breast cancer survivors recruited to participate in the CAMS study. The extensive data has already resulted in multiple papers (described within this report, and attached in the appendix), as well as the additional papers that are in preparation.

Recruitment

DOD funding for the CAMS study was used to expand on prior data already collected for a similar study that was initiated with NCI funding. For all analyses, we combined the data from both the NCI and the DOD studies, therefore the recruitment numbers presented below include participants recruited through both funding sources.

We began recruitment for the first phase of the study with a combined list of 1440 potential subjects from the cancer registries at UCLA and Kaiser Permanente (the West LA and Sunset branches). Of the 1440 invitation letters sent, 411 (28.5%) were found to be either deceased, non-English speakers or not contactable. Among the remaining 1029 potential subjects, 233 (23%) were not interested in participating. Among those interested, 60 (8%) were found to be ineligible upon telephone screening. We then mailed phase one questionnaires to the remaining 736 subjects and after accounting for nonresponders and subsequent ineligibility, we ended up with a final sample of 577 completed questionnaires.

For phase two of the study, we approached women who completed a questionnaire and who lived in California to come in for an in-person visit, which included a blood draw to measure cholesterol and hormone levels, and a DEXA scan to measure bone mineral density (BMD). Among the 526 women we contacted to participate, 494 were both reachable and eligible. Among these eligible women, 148 (30%) were not interested. Of the remaining eligible and interested women, 343 successfully completed the appointment.

Phase three, the neurocognitive study, included recruitment of both BCS and non-BCS control subjects. We sent a total of 134 invitation letters to short-term BCS (2 to 5 years since diagnosis) to come to UCLA for a battery of neurocognitive tests. Of these 134, we were able to make subsequent contact with 123 (92%) women, 70 (57%) of whom were interested in participating. Of the 70 interested women, 11 (16%) were found ineligible during screening, 4 (6%) women did not schedule an appointment, and the remaining 55 were eligible and successfully completed their appointments. A total of 21 control subjects also completed the study, however two of them were subsequently found ineligible. Therefore, our final sample for phase three of the study includes 55 breast cancer survivors and 19 control subjects.

To recruit for phase four, we sent invitation letters to 251 women who were 18 months past their initial BMD to invite them to come in for a follow-up BMD. Among the 222 (88%) women we were able to make subsequent contact with, 43 (19%) were not interested in continuing their participation in the study. Fourteen (6%) women were not eligible because they were not currently cancer free. All of the remaining 165 women who were both eligible and interested completed their appointments.

Subject Characteristics

Demographic and treatment characteristics of the phase one sample by age group are as follows:

Demographic Characteristics of the Sample by Age Group at Diagnosis

	25-34 yrs N=42	35-39 yrs N=93	40-44yrs N=173	45-51 yrs N=269	Total Sample N=577
Current Age Mean yrs (range)	37.9 (30-45)	43.8 (38-50)	48.8 (43.5-55.8)	53.8 (48.2-61.6)	49.5 (30-61.6)
Age at Diagnosis Mean yrs (range)	31.5 (25.2-34.9)	37.7 (35-39.9)	42.9 (40-45)	47.9 (45-51)	43.6 (25.2-51)
Years since Diagnosis Mean yrs (STD)	6.35 (2.0)	6.1 (2.5)	5.9 (2.3)	5.9 (2.3)	5.9 (1.5)
Ethnicity					
White	28 (66.7%)	69 (74.2%)	117 (67.6%)	191 (71.0%)	405 (70.2%)
Black	4 (9.5%)	7 (7.5%)	25 (14.5%)	31 (11.5%)	67 (11.6%)
Hispanic	5 (11.9%)	10 (10.8%)	11 (6.3%)	16 (6.0%)	42 (7.3%)
Asian	3 (7.1%)	5 (5.4%)	17 (9.8%)	24 (8.9%)	49 (8.5%)
Other	2 (4.8%)	2 (2.2%)	3 (1.7%)	7 (2.6%)	14 (2.4%)
Partner Status					
Partnered	27 (64.3%)	69 (74.2%)	125 (72.3%)	184 (68.7%)	405 (70.3%)
Not Partnered	15 (35.7%)	24 (25.8%)	48 (27.7%)	84 (31.3%)	171 (29.7%)
Education					
High school or less	2 (4.8%)	9 (9.7%)	9 (5.2%)	16 (6%)	36 (6.3%)
Vocational training	2 (4.8%)	3 (3.2%)	5 (2.9%)	17 (6.3%)	27 (4.7%)
Some college	13 (31%)	27 (29%)	42 (24.3%)	80 (29.9%)	162 (28.1%)
College graduate	12 (28.6%)	14 (15.1%)	38 (22.0%)	44 (16.4%)	108 (18.8%)
Postgraduate education	13 (31%)	40 (43%)	79 (45.7%)	111 (41.3%)	243 (42.2%)
Income					
<$15,000	0	2 (2.2%)	3 (1.8%)	5 (1.9%)	10 (1.8%)
15-30,000	4 (9.8%)	5 (5.4%)	9 (5.4%)	17 (6.4%)	35 (6.2%)
30,001-45,000	7 (17.1%)	10 (10.8%)	22 (13.1%)	31 (11.7%)	70 (12.4%)
45,001-60,000	5 (12.2%)	13 (14%)	16 (9.5%)	28 (10.6%)	62 (10.9%)
60,001-100,000	14 (35%)	32 (34.4%)	55 (32.7%)	83 (31.3%)	184 (32.5%)
>100,000	11 (26.8%)	31 (37.9%)	63 (37.5%)	101 (38.1%)	206 (36.3%)
Employment Status					
Working full or part-time	33 (78.6%)	77 (82.8%)	137 (79.2%)	209 (77.7%)	456 (79%)
Not working	9 (21.4%)	16 (17.2%)	36 (20.8%)	60 (22.3%)	121 (21%)

Treatment Characteristics of the Sample by Age Group at Diagnosis

	25-34 yrs N=42	**35-39 yrs N=93**	**40-44yrs N=173**	**45-51 yrs N=269**	**Total Sample N=577**
Type of Surgery					
Lumpectomy	22 (52.4%)	53 (57.6%)	88 (50.9%)	158 (59.0%)	321 (55.8%)
Mastectomy	20 (47.6%)	39 (42.4%)	85 (49.1%)	110 (41.0%)	254 (44.2%)
Reconstruction					
Yes	11 (26.2%)	27 (29.0%)	42 (24.4%)	54 (20.2%)	134 (23.3%)
No	31 (73.8%)	66 (71.0%)	130 (75.6%)	214 (79.9%)	441 (76.7%)
Received adjuvant Chemotherapy					
Yes	36 (85.7%)	60 (64.5%)	106 (61.3%)	156 (58.0%)	358 (62.0%)
No	6 (14.3%)	33 (35.5%)	67 (38.7%)	113 (42.0%)	219 (38.0%)
Ever use Tamoxifen					
Yes	5 (11.9%)	26 (28%)	70 (40.5%)	115 (42.8%)	216 (37.4%)
No	37 (88.1%)	67 (72%)	103 (59.5%)	154 (57.2%)	361 (62.6%)
Current Tamoxifen					
Yes	1 (2.4%)	13 (14.8%)	34 (20.4%)	52 (20.0%)	100 (18.0%)
No	40 (97.6%)	75 (85.2%)	133 (79.6%)	208 (80.0%)	456 (82.0%)
Adjuvant Therapy Group					
None	6 (14.3%)	30 (32.3%)	51 (29.5%)	72 (26.8%)	159 (27.5%)
Tam only	0	3 (3.2%)	16 (9.3%)	41 (15.2%)	60 (10.4%)
Chemo only	31 (73.8%)	37 (39.8%)	52 (30.1%)	82 (30.5%)	202 (35.0%)
Tam and Chemo	5 (11.9%)	23 (24.7%)	54 (31.2%)	74 (27.5%)	156 (27.0%)

A more detailed description of this sample can be found in the paper entitled, "Breast Cancer in Younger Women: Reproductive and Late Health Effects of Treatment," which is attached as an appendix.

Key Research Accomplishments

- Patricia Ganz, M.D., completed a paper entitled "Breast cancer in younger women: Reproductive and late health effects of treatment," which was accepted for publication in the *Journal of Clinical Oncology*[6]. The paper provides an overview of phase one and includes the results of the questionnaire analysis. A copy of the paper is attached as an appendix. Briefly, the analysis describes the cohort by age group. Dr. Ganz found that among these breast cancer survivors, physical functioning was quite good, but that the youngest women experienced poorer mental health and less energy. Predictors of better quality of life among the sample included being African American, being married or partnered, and having better emotional and physical functioning. Poorer health perceptions and quality of life were associated with feeling more vulnerable after cancer, and having experienced a menopausal transition as a by-product of therapy.

- Steven Castellon, Ph.D., analyzed the phase three data in his paper, "Cognitive Effects of Adjuvant Therapy," which was recently accepted by the *Journal of Clinical and Experimental Psychology*[7]. The primary aim of Dr. Castellon's paper was to examine whether neurocognitive functioning among breast cancer survivors (BCS) exposed to systemic adjuvant therapy (either chemotherapy alone or chemotherapy and tamoxifen) differs from that seen among BCS who did not receive adjuvant therapy, or from healthy controls. Dr. Castellon found that those BCS who received adjuvant chemotherapy performed significantly worse in the domains of verbal learning, visuospatial functioning and visual memory than BCS not exposed to such therapy. Those BCS who underwent chemotherapy and also used tamoxifen had poorer cognitive function than women without treatment. Those BCS who received no adjuvant therapy appeared to perform as well, and in some cases, better than demographically matched healthy controls. Additionally, self-reported cognitive complaints were not related to objective performance on neurocognitive tasks, although poor cognitive performance was significantly correlated with self-reported mood disturbance (both depression and anxiety) as well as self-reported fatigue.

- In mid-2002, Carolyn Crandall, M.D., applied for and received a New Investigator award from the California Breast Cancer Research Program. This is a three-year award which began on July 1, 2002, and which provides funding for Dr. Crandall to develop her research skills through participating in analyses from this study. Dr. Crandall is being mentored by Drs. Ganz and Greendale, and has already written a paper entitled, "Association of Breast Cancer and its Therapy with Menopause-Related Symptoms," which was recently submitted to the journal *Menopause*[8]. Briefly, the paper describes the prevalence of ten menopause-related

symptoms and the association of these symptoms to current menopause status, as well as to whether the menopause transition was influenced by adjuvant therapy received during breast cancer treatment. In her analysis, Dr. Crandall found a high incidence of hot flashes in all BCS, as well as more severe hot flashes, vaginal dryness and pain with intercourse among post-menopausal women, compared to others. She also found that having transitioned into menopause as a result of breast cancer therapy was associated with worse hot flash severity, independent of current menopause status. Dr. Crandall's subsequent analyses, already underway, will involve data from phases two and four of the study and will examine bone density and its relationship to current menopause status and menopausal transition.

- Dena Herman, Ph.D., also joined our team as an NCI-funded post-doctoral fellow. Dr. Herman has been working with Drs. Ganz and Greendale to examine physical activity and changes in body composition (from DEXA scan data) related to adjuvant therapy. She has completed her first analysis, entitled, "Physical Activity and Weight Gain in Younger Breast Cancer Survivors: Association with Reproductive Health and Quality of Life," which was recently submitted to the journal *Cancer Epidemiology, Biomarkers and Prevention*[9]. Briefly, the paper investigates the predictors of physical activity at work, home and leisure, as well as current weight and BMI (body mass index). Dr. Herman found no relationship between current menopause status and the outcome variables; however she did find that lack of leisure physical activity was associated with both higher weights and BMIs. Dr. Herman is currently working on her next analysis, an investigation of the relationship between physical activity, anthropometric measure, cardiovascular lipids, and blood pressure.

- Amber Pakilit, B.A., took the lead in documenting the CAMS team's experience with recruitment for phase one of this study[10]. She compared recruitment results from a comprehensive cancer center (UCLA) and a community hospital (Kaiser) and showed that breast cancer survivors recruited from the cancer center registry were more likely than those from the community hospital registry to respond to the invitation letter, and were also more likely to return a completed questionnaire. She also found, however, that the community hospital provided access to a more ethnically diverse sample of survivors.

- Suzy O'Donnell, Ph.D., an NCI-funded post-doctoral fellow, is currently working on exploring predictors of complementary and alternative medicine use among the sample.

Reportable Outcomes

Manuscripts

- Pakilit, AT, Kahn, BA, Petersen, L, Abraham, LS, Greendale, GA, Ganz, PA. Making effective use of tumor registries for cancer survivorship research. *Cancer* 2001; 92-5; 1305-1314.

- Ganz, PA, Greendale, GA, Petersen, L, Kahn, BA, Bower, JE. Breast cancer in younger women: Reproductive and late health effects of treatment. *Journal of Clinical Oncology*, in press, November 15, 2003.

- Castellon, SA, Ganz, PA, Bower, JE, Petersen, L, Abraham, L, Greendale, GA. Neurocognitive performance in breast cancer survivors exposed to adjuvant chemotherapy and tamoxifen. *Journal of Clinical and Experimental Psychology*, in revision, October, 2003.

- Crandall, C, Petersen, L, Ganz, PA, Greendale, GA. Association of breast cancer and its therapy with menopause-related symptoms. Submitted to *Menopause*. October, 2003.

- Herman, DR, Ganz, PA, Petersen, L, Greendale, GA. Physical activity and weight gain in younger breast cancer survivors: Association with reproductive health and quality of life. Submitted to *Cancer Epidemiology, Biomarkers and Prevention*. October, 2003.

Editorials

- Ganz, P.A. and G.A. Greendale. Menopause and breast cancer: addressing the secondary health effects of adjuvant chemotherapy. *J Clin Oncol* 19:3303-3305, 2001.

- Ganz, PA, Castellon, SA and Silverman, D. (2002) Estrogen, tamoxifen, and the brain. *Journal of the National Cancer Institute*, 94: 547-549.

Abstracts and Presentations

- G. Greendale, L. Petersen, P.A. Ganz. Bone density in breast cancer survivors. Presented by Dr. Gail Greendale at the 4th International Symposium on Women's Health and Menopause, May 19-23, 2001, Washington, DC.

- Castellon, SA, Ganz, PA, Abraham, L, Bower, JE, Pakilit, AT, Petersen, LP, Greendale, GA. Neurocognitive performance in breast cancer following exposure to adjuvant systemic therapy. Paper presented at the 21st annual meeting of the National Academy of Neuropsychology, San Francisco, CA, November, 2001. Abstract to appear in Archives of Clinical Neuropsychology.

- Herman, DR, Ganz, PA, Petersen, L, Greendale, GA. Physical activity, body mass index and their association with quality of life in younger breast cancer survivors undergoing the menopause transition. Poster presented at the 14th annual meeting of the North American Menopause Society meeting, Miami Beach, FL, September, 2003.

- Crandall, C, Petersen, L, Ganz, P, Greendale, G. Menopause-related symptoms in breast cancer survivors. Poster presented at the 14th annual meeting of the North American Menopause Society meeting, Miami Beach, FL, September, 2003.

Other Funding

- Funding received based on work supported by this award: Dr. Carolyn Crandall received a New Investigator award from the California Breast Cancer Research Program entitled, "Impact of Breast Cancer and its Therapy on Osteoporosis." The award is for three years, starting July 1, 2002, and has allowed Dr. Crandall to analyze data from this study, under the mentorship of Drs. Ganz and Greendale.

- Funding received based on work supported by this award: Dr. Ganz was awarded a grant from the Breast Cancer Research Foundation for "Neuroimaging Correlates of Cognitive Dysfunction After Breast Cancer Treatment." This grant was awarded October, 2001.

- Funding received based on work supported by this award: Dr. Ganz and Dr. Castellon were awarded a grant from the Breast Cancer Research Foundation for "Development of a Computerized Tool to Assess Cognitive Functioning of Breast Cancer Patients in the Clinic." This grant was awarded October, 2003.

Conclusion

The CAMS study began five years ago, with the main goal of recruiting breast cancer survivors to complete a survey reviewing a wide range of issues pertinent to the breast cancer experience and reproductive health. In addition to the survey, we also planned to collect bone density and biologic data on a subset of the women. After the cohort was assembled, additional research questions were explored that were relevant to the sample, e.g. cognitive function. The study data also provided research and training opportunities for several new investigators added to the research team.

Our initial report of the CAMS cohort (JCO in press November 2003) is a description of one of the largest cohorts of younger women survivors with breast cancer ever reported and provides important reference data for health care providers and patients. The JCO has the largest circulation of any oncology journal and therefore we expect widespread impact of these findings. We anticipate important further contributions from the ongoing analyses of the biological data and bone density results. The additional data on cognitive functioning has provided new insights into the late effects of breast cancer

treatment. Most of our findings are re-assuring and can allow younger women with breast cancer to understand whether or not there are any serious late effects from their treatments. These issues become more critical as the size of breast cancers has become smaller and the risks of therapy may outweigh the benefits. The information generated in this study will help providers and patients make informed treatment decisions in the future.

REFERENCES

1. Colditz, G.A. Hormone replacement therapy increases the risk of breask cancer. *Ann NY Acad Sci* 833: 129-136, 1997.

2. Colditz, G.A. Relationship between estrogen levels, use of hormone replacement therapy, and breast cancer. *J Nat Cancer Inst* 90: 814-823, 1998.

3. Colditz, G.A. Hormones and breast cancer: evidence and implications for consideration of risks and benefits of hormone replacement therapy. *J Womens Health* 8: 347-357, 1999.

4. Burstein, H.J. and E.P. Winer. Primary care for survivors of breast cancer. *N Engl J Med* 343: 1086-1094, 2000.

5. Shapiro, C.L. and A. Recht. Side effects of adjuvant therapy of breast cancer. *N Engl J Med* 344: 1997-2008, 2001.

6. Ganz, PA, Greendale, GA, Petersen, L, Kahn, BA, Bower, JE. Breast cancer in younger women: Reproductive and late health effects of treatment. Accepted for publication in the *Journal of Clinical Oncology*, August, 2003.

7. Castellon, SA, Ganz, PA, Bower, JE, Petersen, L, Abraham, L, Greendale, GA. Neurocognitive performance in breast cancer survivors exposed to adjuvant chemotherapy and tamoxifen. Accepted for publication in the *Journal of Clinical and Experimental Psychology,* October, 2003.

8. Crandall, C, Petersen, L, Ganz, PA, Greendale, GA. Association of breast cancer and its therapy with menopause-related symptoms. Submitted to *Menopause*, October, 2003.

9. Herman, DR, Ganz, PA, Petersen, L, Greendale, GA. Physical activity and weight gain in younger breast cancer survivors: Association with reproductive health and quality of life. Submitted to *Cancer Epidemiology, Biomarkers and Prevention*, August, 2003.

10. Pakilit, AT, Kahn, BA, Petersen, L, Abraham, LS, Greendale, GA, Ganz, PA. Making effective use of tumor registries for cancer survivorship research. *Cancer* 2001; 92-5; 1305-1314.

List of Personnel

Patricia Ganz, P.I.
Gail Greendale, Co-P.I.
Julienne Bower
Steven Castellon
Amber Pakilit
Laura Petersen
Laura Zibecchi

balt5/lj-jco/lj-jco/lj2203/lj0742-03a | wilkerss | S=5 | 9/22/03 | 13:28 | Art: 04196 | Input-JB

AQ: A

Breast Cancer in Younger Women: Reproductive and Late Health Effects of Treatment

By Patricia A. Ganz, Gail A. Greendale, Laura Petersen, Barbara Kahn, and Julienne E. Bower

Purpose: **In 1997, we initiated a cohort study to evaluate quality of life (QOL) and reproductive health outcomes in younger female breast cancer survivors.**

Materials and Methods: **Using listings from two tumor registries, we recruited women with stage 0, I, or II breast cancer who were 50 years or younger at diagnosis and disease-free survivors for 2 to 10 years. A mailed survey questionnaire assessed medical and demographic factors, health-related QOL, mood, outlook on life, and reproductive health outcomes.**

AQ: B

Results: **We recruited 577 women, who ranged in age from 30 to 61.6 years (mean, 49.5 years) and were surveyed approximately 6 years after diagnosis. Almost three fourths had received some form of adjuvant therapy. Amenorrhea occurred frequently as a result of treatment in women ≥ 40 years at diagnosis, and treatment-associated menopause was associated with poorer health perceptions. Across the cohort, physical functioning was quite good, but the youngest women experienced poorer mental health ($P = .0002$) and less vitality (energy; $P = .03$). Multiple regression analyses predicting QOL demonstrated better outcomes in African-American women, married or partnered women, and women with better emotional and physical functioning, whereas women who reported greater vulnerability had poorer QOL.**

Conclusion: **Overall QOL in younger women who survive breast cancer is good, but there is evidence of increased emotional disruption, especially among the youngest women. Factors that may contribute to poorer health perceptions and QOL include experiencing a menopausal transition as part of therapy, and feeling more vulnerable after cancer.**

J Clin Oncol 21:●●●-●●●.

BREAST CANCER is primarily a disease of older women; only approximately 25% of incident cases occur in women younger than 50 years.[1] However, the population bulge in this age group has increased the absolute number of younger women diagnosed with breast cancer in recent years. During the last decade the mortality rate from breast cancer has steadily declined, with the greatest gains among younger women, largely resulting from more widespread application of adjuvant therapy.[2] Thus, this expanding population of breast cancer survivors deserves our attention.

The literature suggests that adaptation and quality of life (QOL) after breast cancer diagnosis is more difficult for younger women.[3-6] On standardized measures of depression and QOL, younger women often show greater changes in mood and poorer emotional functioning than older women,[7-9] and they appear to experience more difficulties and disruptions from the disease and its treatments because of child rearing activities and employment outside the home.[10] There are also important reproductive health effects of adjuvant therapy that specifically affect younger women (eg, infertility and early menopause).[11,12]

In 1997, we initiated the Cancer and Menopause Study (CAMS) to evaluate the QOL and health outcomes of younger female survivors of breast cancer, with a specific focus on the reproductive and late health effects of treatment. The study was conducted in two phases: first, a survey focused on QOL and health outcomes; second, an in-person visit evaluated biomedical outcomes, including anthropometric measurements, blood pressure, cardiovascular lipids, reproductive hormones, and measurement of bone mineral density and body composition. Additional substudies focused on cognitive functioning and longitudinal assessment of bone density. This report introduces the CAMS study cohort and presents the main findings from the survey phase. Future reports will elaborate on other findings from the survey, such as the relationship between menopausal status and symptoms, as well as the prevalence and predictors of fatigue and physical activity in this cohort.

MATERIALS AND METHODS

Study Design

The National Cancer Institute Office of Cancer Survivorship provided initial funding for this study, and as a result, the initial goals of the study were to examine the feasibility of recruiting long-term cancer survivors (5 to 10 years after diagnosis) from the cancer center's tumor registry, and to

From the University of California Los Angeles (UCLA) Schools of Medicine and Public Health; Division of Cancer Prevention & Control Research, Jonsson Comprehensive Cancer Center at UCLA; Division of Geriatrics, Department of Medicine, and Department of Psychiatry and Biobehavioral Medicine, David Geffen School of Medicine at UCLA; Cousins Center for Psychoneurimmunology, UCLA Neuropsychiatric Institute, Los Angeles, CA.

Submitted April 29, 2003; accepted August 25, 2003.

Supported by funding from the National Cancer Institute (P30 CA16042), the Susan G. Komen Foundation, and the US Department of Defense (DAMD 17-98-1-1810). P.A.G. was also supported through an American Cancer Society Clinical Research Professorship.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

Address reprint requests to Patricia A. Ganz, MD, Division of Cancer Prevention and Control Research, UCLA Jonsson Comprehensive Cancer Center, A2-125 CHS, Box 956900, Los Angeles, CA 90095-6900; e-mail: pganz@ucla.edu.

0732-183X/03/2122-1/$20.00

describe the effects of breast cancer treatments on gonadal function in younger women. Additional funding from the Department of Defense Breast Cancer Research Program allowed expansion of the study to breast cancer survivors 2 to 5 years after diagnosis and inclusion of survivors from a community hospital. The overall goal of the study was to have a sufficiently large sample of younger breast cancer survivors with stage 0, I, and II disease to examine the relationship between specific treatments and reproductive health outcomes.

Recruitment Procedures

Recruitment for CAMS from the two hospital tumor registries was described in detail by Pakilit et al.[13] Briefly, after obtaining institutional review board approval for this research at both hospitals, we obtained listings of women diagnosed with breast cancer between 1987 and 1993 for the 5- to 10-year sample and between 1994 and 1997 for the 2- to 5-year sample. Patients were eligible for enrollment onto this study if they had a diagnosis with first invasive or noninvasive breast cancer (ductal carcinoma-in-situ) at 50 years of age or younger; were alive and disease-free; had no cancer before the breast cancer diagnosis; and had stage 0, I, or II disease according to the tumor registry records. The tumor registries provided information about diagnosis date, date of birth, race or ethnicity, vital status, address, and phone number for each potentially eligible woman.

Study invitation letters, written on the letterhead of a physician from the respective institutions, were mailed to all potentially eligible women along with a postage-paid response form to indicate interest in participating in the survey study. We excluded women who did not reside in the United States. For returned letters, attempts were made to update addresses through the hospital databases, and repeat mailings were performed. A second mailing was done at 2 weeks if there was no response; however, the research protocol was subsequently modified to allow a phone call to all nonrespondents. If the woman could not be reached after multiple attempts, she was classified as unreachable.

Interested women were screened by telephone to confirm study eligibility (ability to read and understand English, being disease-free without a recurrence) and to describe the research in more detail. If eligible and interested in participation, the woman was mailed the study survey with a postage-paid return envelope, along with an informed consent form for signature. Systematic reminders (mail and phone) were used to ensure return of the surveys (details are provided in Pakilit et al[13]).

Instruments

The 45-page survey included demographic information; past health and medical history; current symptoms; current and past medications; alternative health practices; tobacco and alcohol use; weight and weight changes; height; breast cancer treatments; menstrual and menopause history; pregnancy or infertility and contraceptives; bladder problems; osteoporosis or fracture history; physical activity; sexual activity; depressive symptoms, mood, fatigue, and QOL; vulnerability; and meaning related to the cancer experience. We describe below the specific instruments included in this report.

Demographic and breast cancer treatment information (type of surgery, chemotherapy, radiation therapy, and tamoxifen) were obtained using questions from a series of prior studies.[7,9,10] Only surgical treatment information was reliably available from the tumor registry databases.[14,15] Nineteen comorbid conditions were queried with the following response choices: "no, never," "yes, in past (> 1 year ago)," and "yes, now (during the past year)." If the response was "yes," respondents indicated whether medication was currently being taken for the condition. Conditions ranged from serious events such as stroke and heart attack, to thyroid conditions, diabetes, high blood pressure, depression, and osteoarthritis. The Breast Cancer Prevention Trial Symptom Checklist,[16,17] a list of 42 everyday problems (such as hot flashes, headaches, vaginal dryness, breast tenderness) was used to describe current symptoms. Respondents rated how much they were bothered by each symptom during the last 4 weeks on a 5-point Likert-type severity scale from 0 (not at all) to 4 (extremely). This scale also has been used with breast cancer survivors to evaluate menopausal symptoms.[9,18]

Reproductive history and menopausal status were assessed through a series of questions adapted from the Study of Women Across the Nation.[19] These questions ascertained current, precancer, and immediate postcancer menstrual histories, and whether menstrual periods stopped as a result of cancer treatments. Premenopausal was defined as regular menstrual periods, perimenopausal was defined as irregular periods or periods that stopped for 3 months or more and then resumed, and postmenopausal was defined as complete cessation of menstrual periods at least 6 months for current status and ≥ 12 months for status before cancer. Women with a bilateral oophorectomy were also classified as postmenopausal. Menopause status could not be classified in women taking exogenous hormones or after simple hysterectomy. A treatment-related menopause transition was considered present when menstrual status changed from one category before diagnosis to a different category after breast cancer treatments. Gynecologic surgical history, including hysterectomy and unilateral and bilateral oophorectomy, was ascertained for the time before and after the cancer diagnosis. Pregnancy history and outcomes were queried (number of live births, miscarriages, stillbirths, ectopic pregnancies, and abortions), as well as whether the pregnancies occurred before, after, or both before and after the breast cancer diagnosis.

The RAND SF-36 (also known as the MOS-SF-36)[20,21] and the Ladder of Life Scale[22] were used to assess health-related QOL. The MOS- SF-36 contains eight individual scales: physical functioning; role function, physical; bodily pain; social functioning; emotional well-being; role function, emotional; vitality (energy and fatigue); and general health perceptions[20,21] Each scale is scored from 0 to 100, with 100 being the most favorable score. General population norms are available for the SF-36.[23] The SF-36 can also be scored as two summary scales: a Physical Component Summary Scale and a Mental Component Summary Scale (MCS).[24] These scales are scored in reference to a normal population whose mean score is set at 50, with a score of 60 or 40 representing 1 standard deviation (SD) above or below the mean, respectively.[24] The Ladder of Life scale[22,25] has been widely used in epidemiologic and population studies and provides a global single-item QOL score. Ratings are made on a 10-point scale ranging from worst possible life to best possible life.

Depressive symptoms and affect were measured with two instruments. The Center for Epidemiologic Studies–Depression Scale (CES-D) is a reliable and valid 20-item self-report scale developed for the general population to measure depressive symptoms over the last week.[26] Normative data are available for healthy women.[16,27-29] Higher scores indicate greater risk of depression, with scores ≥ 16 indicating an increased risk of clinical depression.[26] We also used the Positive and Negative Affect Schedule (PANAS),[30] a 20-item adjective checklist that has excellent reliability and validity,[30] and uses a 5-point Likert-type scale for rating 20 mood states in the last 4 weeks. The instrument yields both positive affect and negative affect subscale scores.

The Sexual Activity Questionnaire[31] is a reliable and valid scale that was developed for the British tamoxifen prevention trial for use with healthy women at risk for breast cancer[32] and also has been used with breast cancer survivors.[10] The Sexual Activity Questionnaire has three scales: pleasure, discomfort, and habit (frequency of activities). Higher scores on each scale indicate greater pleasure, more discomfort, and greater frequency of activities.

In an earlier study of breast cancer survivors, we developed a 12-item scale to measure perceptions of life after cancer, on the basis of a review of the literature, focus groups with cancer survivors, and clinical experience.[9] Example items include "Surviving breast cancer has changed my outlook on life," "I get less worried about trivial things," and "I feel more vulnerable now, as if the world is a more dangerous place." Respondents indicate the extent to which they believe their outlook has changed on a 5-point scale, ranging from 0 (not at all) to 4 (very much). Factor analysis in the original sample[9] yielded two factors. The first factor includes six items assessing changes in perspectives and priorities and was used as a measure of positive meaning. The second factor includes six items assessing fears about recurrence and about one's body, and was used as a measure of vulnerability.

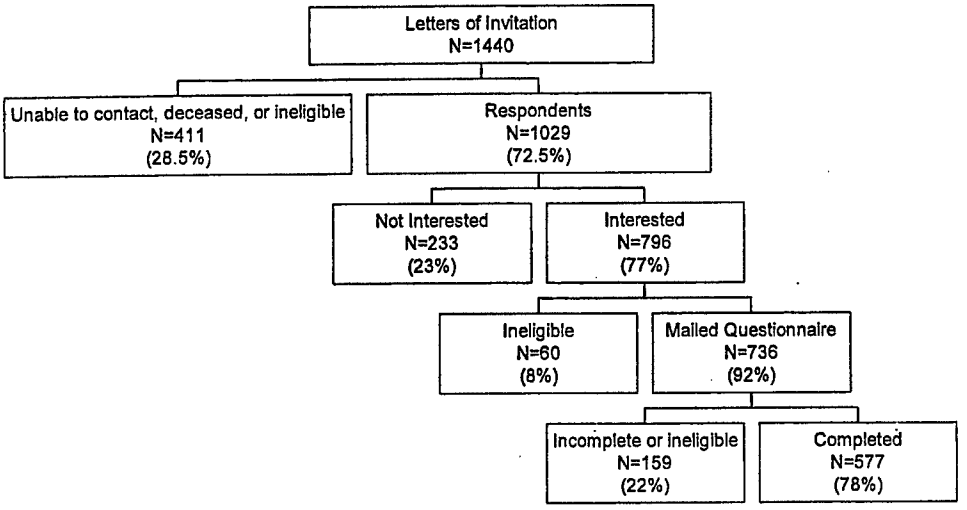

Fig 1. Results of recruitment of patients invited to complete survey from two tumor registries.

Statistical Considerations

Statistical analyses were done using Statistical Analysis Software version 6.04 (SAS/STAT User's Guide, Version 6, SAS Institute, Cary, NC, 1990). AQ: H χ^2 tests were used to compare the distribution of medical and demographic categoric variables across age groups. One-way analysis of variance was used to compare medical and quality-of-life continuous variables across age groups. Analysis of covariance was used to create and compare least-squares means of QOL variables by adjuvant therapy group, adjusting for age, time since diagnosis, race, current tamoxifen use, and current menopausal status. Linear regression was used to model general health perceptions and the ladder of life.

RESULTS

Recruitment Results

F1 Recruitment results are shown in Figure 1. Briefly, we received data for 1,454 potentially eligible women from the two tumor registries. Fourteen were excluded (incorrect histology or duplicate listings), for an initial mailing to 1,440 women. Mailed AQ: I responses from 72.5% (N = 1,029) were received; 77% of these women expressed interest in participating in the study. Of these, 8% were ineligible, leading to a survey mailing to 736 women. From this sample, 577 women returned usable questionnaires and they comprise the study cohort for this report (final response, 56%; 577 of 1,029 potentially eligible respondents).

We made multiple attempts to contact the nonrespondents (Pakilit et al.[13]). Of the 411 nonrespondents, 84% could not be contacted by either telephone or mail, 7% were found to be AQ: J deceased, and 9% were ineligible because of language. We observed a significantly higher response rate to our invitation letter for women recruited from the cancer center registry (75.4% *v* 65.4%; $P < .0001$), as well as a higher response rate from white ($P = .003$) and more recently diagnosed women ($P = .01$). These same demographic characteristics were significantly related to agreement to be mailed the study survey. The final sample of 577 included 415 women recruited from the cancer center from 873 invitations mailed, and 162 from the community hospital from 567 invitations mailed.

Description of the Study Cohort

Demographic characteristics by age at diagnosis are shown in Table 1. Women ranged in age from 25 to 51 years at diagnosis, AQ: K with a current age range of 30 to 61.6 years. The survey was completed at an average of about 6 years after breast cancer diagnosis. The cohort was ethnically diverse, reflecting the population of younger women with breast cancer in Los Angeles. The majority were in a partnered relationship, working full or part time, with high levels of education and income. Most received breast conserving surgery (55.8%) and about three fourths received some form of adjuvant therapy (Table 2). T2 Chemotherapy was used significantly more often in the youngest women (86%; $P = .007$), and there was a significant positive relationship between tamoxifen use and older age ($P = .0003$). About one fourth of the women in the sample received both chemotherapy and tamoxifen adjuvant therapy, with 18% currently taking tamoxifen.

There were low rates of current or past comorbid conditions. Few women had a history of cardiovascular disease (stroke, < 1%; myocardial infarction, < 1%); however, 15% had a history of current or past hypertension, and 3.5% reported a history of current or past diabetes. More commonly reported conditions were migraine headaches (31%), anemia (31%), depression (34%), uterine fibroids (27%), hypothyroidism (16%), hyperthyroidism (5%), and asthma (10%). A small number of women reported a past or present diagnosis of arthritis (osteoarthritis, 7%; rheumatoid arthritis, 3%).

Menopause, Reproductive, and Fertility Findings

Table 3 shows menopausal status by age group at diagnosis T3 and survey completion. At diagnosis, the majority of women in all age groups were menstruating (pre- or perimenopausal). An average of 6 years later, there were substantial shifts in menstrual status; the majority who were ≥ 40 years old at diagnosis were postmenopausal at survey. These findings are consistent with the predictive model developed by Goodwin et al.[12] At survey, 14%

Table 1. Demographic Characteristics of the Sample by Age Group at Diagnosis

Demographic Characteristic	Age at Diagnosis (years) 25-34 (n = 42) No.	%	35-39 (n = 93) No.	%	40-44 (n = 173) No.	%	45-51 (n = 269) No.	%	Total Sample (N = 577) No.	%	P
Current age, years											< .0001
Mean	37.9		43.8		48.8		53.8		49.5		
Range	30-45		38-50		43.5-55.8		48.2-61.6		30-61.6		
Age at diagnosis, years											< .0001
Mean	31.5		37.7		42.9		47.9		43.6		
Range	25.2-34.9		35-39.9		40-45		45-51		25.2-51		
Years since diagnosis											.52
Mean	6.35		6.1		5.9		5.9		5.9		
Standard deviation	2.0		2.5		2.3		2.3		1.5		
Ethnicity											
White	28	66.7	69	74.2	117	67.6	191	71.0	405	70.2	.66*
African-American	4	9.5	7	7.5	25	14.5	31	11.5	67	11.6	
Hispanic	5	11.9	10	10.8	11	6.3	16	6.0	42	7.3	
Asian	3	7.1	5	5.4	17	9.8	24	8.9	49	8.5	
Other	2	4.8	2	2.2	3	1.7	7	2.6	14	2.4	
Partner status											
Partnered	27	64.3	69	74.2	125	72.3	184	68.7	405	70.3	.56
Not partnered	15	35.7	24	25.8	48	27.7	84	31.3	171	29.7	
Education											
High school or less	2	4.8	9	9.7	9	5.2	16	6	36	6.3	.36
Vocational training	2	4.8	3	3.2	5	2.9	17	6.3	27	4.7	
Some college	13	31	27	29	42	24.3	80	29.9	162	28.1	
College graduate	12	28.6	14	15.1	38	22.0	44	16.4	108	18.8	
Postgraduate education	13	31	40	43	79	45.7	111	41.3	243	42.2	
Income, $											
< 15,000	0		2	2.2	3	1.8	5	1.9	10	1.8	.65†
15-30,000	4	9.8	5	5.4	9	5.4	17	6.4	35	6.2	
30,001-45,000	7	17.1	10	10.8	22	13.1	31	11.7	70	12.4	
45,001-60,000	5	12.2	13	14	16	9.5	28	10.6	62	10.9	
60,001-100,000	14	35	32	34.4	55	32.7	83	31.3	184	32.5	
> 100,000	11	26.8	31	37.9	63	37.5	101	38.1	206	36.3	
Employment status											
Working full or part time	33	78.6	77	82.8	137	79.2	209	77.7	456	79	.78
Not working	9	21.4	16	17.2	36	20.8	60	22.3	121	21	

*P value for ethnicity compares white with nonwhite.

†P value for income compares < $45,000 v $45,000 v $45,000-$75,000 v > $75,000.

of the cohort reported having had a hysterectomy, which was most prevalent in the two oldest age groups (data not shown). Only 7% of women in the sample had received a bilateral oophorectomy (n = 40), and in half of this group it was performed after the diagnosis of breast cancer.

Pregnancy with at least one live birth was reported in 373 (65%) of the survey respondents (Table 3). Only 5% of women reported a pregnancy and live birth after the breast cancer diagnosis. Twenty percent reported that before breast cancer they were planning or hoping to have children, and 11% (n = 61) reported that they had considered getting pregnant since the breast cancer diagnosis. For these 61 survivors, 19% reported that they were not planning a pregnancy as a result of physician recommendation, 17% said they were not planning a pregnancy because they were worried about the risks, and 29% said they were not planning a pregnancy for other reasons that were primarily related to age or their personal relationship situation (categories were not mutually exclusive). However, 7% reported that they had been trying to become pregnant, 17% reported that they did become pregnant, and 12% indicated that they had specific plans or fertility treatments underway (categories were not mutually exclusive). Fifteen percent indicated that they were still considering a pregnancy and that they were undecided.

Current Symptoms

These survivors reported a wide range of everyday symptoms. Figures 2 to 4 show the prevalence (any rating of bother, compared with none) of various symptoms by age group at diagnosis. Hot flashes and night sweats occurred less often in the youngest women, and increased with age (Fig 2). As in our previous studies using this symptom checklist,[9,16] complaints of weight gain and being unhappy with body appearance were exceedingly common and were not specific for age group. Breast sensitivity was most frequently reported in the youngest women. Genitourinary symptoms are shown in Figure 3. An age relationship was most notable for vaginal dryness and dyspareunia, likely paralleling changes in menopausal status. These findings are consistent with earlier reports.[9,16] Urine loss with sneezing or

F4

Table 2. Medical Characteristics of the Sample by Age Group at Diagnosis

Medical Characteristic	Age at Diagnosis (years) 25-34 (n = 42) No.	%	35-39 (n = 93) No.	%	40-44 (n = 173) No.	%	45-51 (n = 269) No.	%	Total Sample (n = 577) No.	%	P
Type of surgery											
Lumpectomy	22	52.4	53	57.6	88	50.9	158	59.0	321	55.8	.38
Mastectomy	20	47.6	39	42.4	85	49.1	110	41.0	254	44.2	
Reconstruction											
Yes	11	26.25	27	29.0	42	24.4	54	20.2	134	23.3	.32
No	31	73.8	66	71.0	130	75.6	214	79.9	441	76.7	
Received adjuvant chemotherapy											
Yes	36	85.7	60	64.5	106	61.3	156	58.0	358	62.0	.007
No	6	14.3	33	35.5	67	38.7	113	42.0	219	38.0	
Ever use tamoxifen											
Yes	5	11.9	26	28	70	40.5	115	42.8	216	37.4	.0003
No	37	88.1	67	72	103	59.5	154	57.2	361	62.6	
Current tamoxifen*											
Yes	1	2.4	13	14.8	34	20.4	52	20.0	100	18.0	.03
No	40	97.6	75	85.2	133	79.6	208	80.0	456	82.0	
Adjuvant therapy/group											
None	6	14.3	30	32.3	51	29.5	72	26.8	159	27.5	< .0001
Tamoxifen only	0		3	3.2	16	9.3	41	15.2	60	10.4	
Chemotherapy only	31	73.8	37	39.8	52	30.1	82	30.5	202	35.0	
Tamoxifen and chemotherapy	5	11.9	23	24.7	54	31.2	74	27.5	156	27.0	

*Information on current tamoxifen missing for 21 women.

coughing also increased in frequency with age. Despite the low rate of arthritis as a comorbid condition in this sample, many women complained of general aches and pains, joint pains, and muscle stiffness (Fig 4), which seems to be age related, as described in earlier studies.[9,16] Complaints of forgetfulness and difficulty concentrating were reported in 35% to 65% of the women in the sample, unrelated to age. For comparison, data from healthy women age 35 to 49 entering the Breast Cancer Prevention Trial, using the same symptom checklist, showed 59.8% who were unhappy with appearance, 58.3% with breast sensitivity, 43.5% with general aches and pains, 34.6% with muscle stiffness, and 26% with hot flashes.[16]

AQ: L

QOL Outcomes

Table 4 presents QOL outcomes by age at diagnosis. Overall, these women reported high levels of physical functioning on the individual subscales of the SF-36 and the Physical Component Summary Scale. However, there were substantial decrements in the vitality (energy) scale score, with the lowest scores in the youngest age group (P = .03). For these women, the vitality

AQ: M

Table 3. Menstrual and Reproductive History by Age Group at Diagnosis

Menstrual and Reproductive History	Age at Diagnosis (years) 25-34 (n = 42) No.	%	35-39 (n = 93) No.	%	40-44 (n = 173) No.	%	45-51 (n = 269) No.	%	Total sample (n = 577) No.	%
Menstrual status before diagnosis										
Premenopausal	39	93	80	86	136	79	137	51	392	68
Perimenopausal	3	7	9	10	17	10	58	22	87	15
Postmenopausal	0		0		11	6	39	15	50	9
Unclassifiable	0		4	4	9	5	35	13	48	8
Menstrual status at time of survey										
Premenopausal	25	60	36	39	23	13	7	3	91	16
Perimenopausal	10	24	16	17	33	19	17	6	76	13
Postmenopausal	4	10	34	37	101	58	207	77	346	60
Unclassifiable	3	7	7	8	16	9	38	14	64	11
History of live births*										
All before cancer	11	58	45	85	111	99	189	100	356	95
All after cancer	1	5	2	4	0		0		3	1
Before and after cancer	7	37	6	11	1	1	0		14	4

*25-34 years (n = 19), 35-39 years (n = 53), 40-44 years (n = 112), 45-51 (n = 269), total sample (n = 577).

balt5/lj-jco/lj-jco/lj2203/lj0742-03a | wilkerss | S=5 | 9/22/03 | 13:28 | Art: 04196 | Input-JB

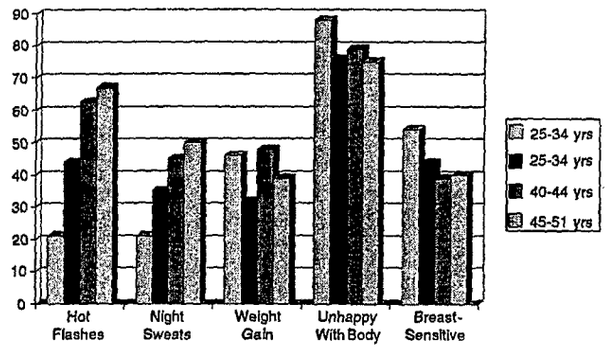

Fig 2. Prevalence (reported in percentage) of vasomotor symptoms, weight gain, body image, and breast sensitivity by age at breast cancer diagnosis.

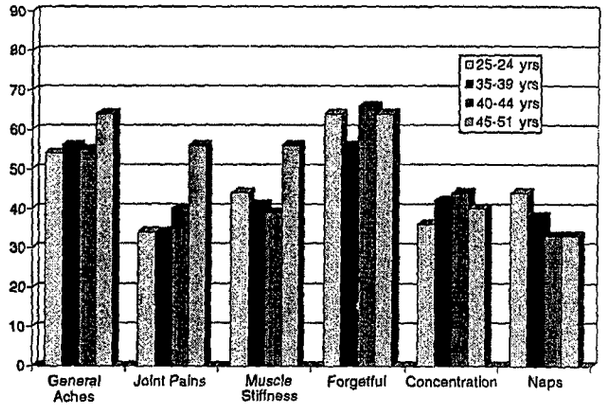

Fig 4. Prevalence (reported in percentage) of musculoskeletal complaints, cognitive complaints, and naps by age at breast cancer diagnosis. Gen, general; Stiff, stiffness.

scale score is approximately 0.5 SD below normal for that age group.[20] Social and emotional functioning scores were lowest in the youngest women ($P = .007$ for social; $P = .009$ for emotional), with an age-related gradient in these scales. Similarly, on the MCS, the youngest women were more than 0.5 SD below the population norm for that measure ($P = .0002$). Scores on the CES-D and the PANAS are consistent with the SF-36 emotional functioning scale, with more depressive symptomatology, lower positive affect, and more negative affect in the youngest women. Ladder of Life scores did not differ by age, nor were there age-related differences in sexual functioning or outlook on life.

Additional analyses were conducted to explore the age differences in mental health. We hypothesized that younger women would be more adversely affected by cancer-related changes that were age-inappropriate, specifically going through menopause. We evaluated the association between the menopausal transition and the MCS scores in each age group. Results showed that among women aged 24 to 34 years at diagnosis, those who went through menopause after cancer treatment reported significantly lower MCS scores (mean, 41.9; SD, 14.5) than those who did not go through menopause (mean, 48.1; SD, 9.1), although this difference did not reach statistical significance ($P = .10$). In contrast, MCS scores in the older age categories of this cohort were not related to the development of menopause.

We next examined the QOL outcomes according to the type of adjuvant therapy that had been received. Because treatments were significantly different across the age groups (Table 2), age was controlled for in the analysis, along with years since diagnosis, ethnicity, current tamoxifen use, and current menopausal status, all of which were significantly different in univariate comparisons. We found no significant differences by treatment group, with the exception of the positive affect scale of the PANAS ($P = .02$), with patients receiving no treatment having the lowest scores on this scale. A similar but nonsignificant pattern was seen for the CES-D ($P = .08$) and the Ladder of Life ($P = .08$). Importantly, there were no significant differences associated with treatment for physical or emotional well-being, or sexual functioning (data not shown).

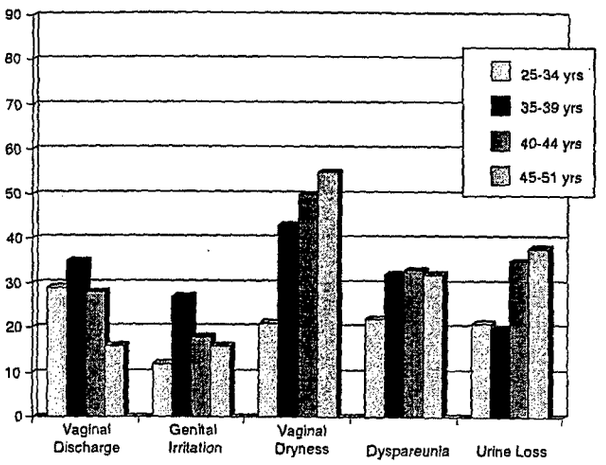

Fig 3. Prevalence (reported in percentage) of genitourinary symptoms by age at breast cancer diagnosis. Vag, vaginal.

Predictors of QOL

As in our previous work with long-term survivors of breast cancer,[10] we examined the SF-36 general health perceptions scale and the Ladder of Life scale in multivariate models. Three groupings of predictors were used in our models: demographic measures (age, ethnicity, education, income, employment status, and partnership status), treatment (time since diagnosis, type of surgery, chemotherapy, tamoxifen, and chemotherapy with tamoxifen), particular aspects of QOL and health status (number of health conditions, emotional well-being, physical functioning, and vulnerability), and reproductive health factors (current menopausal status and treatment-related menopausal transition). We hypothesized that cancer treatment–related variables would not be strongly associated with the dependent variables, but needed to be controlled for, whereas self-rated dimensions of well-being (physical, emotional, and vulnerability) would contribute significantly to subjective assessments of QOL.

Table 5 shows the results of the multivariate regression models. For the general health perceptions scale model, better T5

Table 4. Quality of Life Assessments by Age Group at Diagnosis

Quality of Life Assessment	Age at Diagnosis (years) 25-34 (n = 42) Mean	SD	35-39 (n = 93) Mean	SD	40-44 (n = 173) Mean	SD	45-51 (n = 269) Mean	SD	Total Sample (n = 577) Mean	SD	P
MOS-SF-36											
Physical	88.2	17.9	86.1	17.9	85.2	19.9	82.5	20.3	84.3	19.7	.16
Role physical	83.3	33	78.5	34.9	80.8	34.2	77.7	35.7	79.2	34.9	.69
Role emotional	73.8	38.6	74.6	36.2	77.9	36.1	82.2	31.5	79.1	34.3	.17
Vitality	49.8	23.0	55.8	22.5	58.8	20.6	59.7	21.9	58.1	21.8	.03
Emotional	69.3	19.5	72.3	18.6	74.0	17.4	77.3	17.4	74.9	17.9	.009
Social	75.3	25	80.4	23.4	84.2	21.8	86.2	20.2	83.9	21.8	.007
Pain	77.7	24.6	76.2	23.6	80.7	20.9	77.7	21.5	78.4	21.9	.39
General health	70.8	24	69.8	20.7	72.9	21.3	72.6	20.2	72.1	20.9	.64
PCS	52.0	11	50.5	9.1	51.1	9.4	49.2	9.4	50.2	9.5	.10
MCS	44.7	12.6	47.4	11.7	48.9	10.4	51.2	9.6	49.4	10.6	.0002
CES-D											
Mean	13.4	11.8	12.9	10.6	11.2	9.7	10.2	9.9	11.2	10.1	.06
Percentage of patients scoring ≥ 16	28.6		31.2		24.4		24.2		25.7		.55
PANAS											
Positive affect	31.8	7.9	34.1	8	34.8	8.0	35.4	8.0	34.8	8.0	.04
Negative affect	19.6	8.1	18.8	7.6	17.6	6.5	16.9	6.5	17.6	6.9	.03
Sexual activity questionnaire*											
Pleasure	14.2	4.2	13.0	4.4	12.8	4.4	12.6	4.5	12.9	4.5	.33
Discomfort	1.6	1.7	2.4	2.2	2.6	2.3	2.7	2.1	2.5	2.2	.08
Habit	1.9	0.7	2.0	0.6	1.9	0.7	2.0	0.5	1.9	0.6	.86
Ladder of Life Score	7.0	2.1	7.2	1.8	7.5	1.9	7.6	1.8	7.4	1.9	.10
Outlook on life											
Meaning	13.8	6.1	13.9	5.4	14.8	5.7	13.4	5.7	13.9	5.7	.11
Vulnerability	6.6	4.2	6.5	4.5	7.0	4.5	6.2	4.8	6.5	4.6	.41

Abbreviations: SD, standard deviation; MOS-F, ???; PCS, Physical Component Summary Scale; MCS, Mental Component Summary Scale; CES-D, Center for Epidemiologic Studies—Depression Scale; PANAS, Positive and Negative Affect Schedule.

*The items in this questionnaire were answered only by women who were currently sexually active, n = 358.

physical and emotional functioning and higher education (≥ high school) were significantly associated with better health perceptions. However, feeling more vulnerable, having more comorbid conditions, and having gone through menopause after breast cancer treatment were significantly associated with poorer health perceptions. This model was robust, with an adjusted R^2 = 0.45. When the Ladder of Life was used as the dependent variable in the model, better QOL was significantly associated with being African-American (compared with being white), being married or in a partnered relationship, and having better physical and emotional functioning. Education demonstrated a U-shaped relationship to QOL, with women having vocational or partial college education showing poorer scores than women with a high school education or less and women with a college education or higher. In this model as well, feeling more vulnerable after cancer was significantly associated with a poorer evaluation of QOL. This model also was robust, with an adjusted R^2 = 0.46.

DISCUSSION

In a series of research studies with breast cancer patients and survivors during the last 15 years, we have consistently observed that younger women with breast cancer were at greater risk for psychologic distress than older women,[7-9,33] and were at an increased risk for fatigue.[34] They also seem to be at greater risk for sexual dysfunction, especially in association with treatment-related changes in menstrual status.[9,35] These earlier studies included women whose average age at diagnosis was about 55 years. Our findings related to psychologic distress and younger age have been replicated by others.[3,36,37]

Some of these issues were recognized, and a decade ago the National Institutes of Health sponsored a special conference on Breast Cancer in Younger Women, the proceedings of which were published in 1994.[38] In addition to reviewing the epidemiology, risk factors, and predictors of outcome in younger women, the conference reviewed the late effects of adjuvant therapy in younger women,[39] a range of reproductive health issues,[40-42] and psychosocial issues and survival.[4,43-45] As a result of that conference, considerable interest and funding opportunities were generated related to examination of the special concerns of younger women with breast cancer. The CAMS research program introduced in this article is a direct result of those efforts.

To date, there are few published studies focusing specifically on younger women with breast cancer.[5,46,47] Both Bloom et al[5] and Allen et al[47] recruited cohorts of newly diagnosed younger women with breast cancer as part of intervention studies designed to address specific psychosocial needs and concerns of younger women. An additional study describes an inception cohort of 183 premenopausal breast cancer patients who were

Table 5. Predictors of Two Linear Regression Models for Quality of Life: General Health Perceptions and Ladder of Life

	Dependent Variable					
	General Health Perceptions			Ladder of Life		
Model-adjusted value R^2	0.45			0.46		
P*	< .0001			< .0001		
Parameter estimates	Coefficient (β)	SE	P†	Coefficient (β)	SE	P†
Intercept	12.91	9.38	.17	1.74	0.85	.04
Age at survey, years	0.28	0.17	.10	0.02	0.02	.25
Ethnicity, African-American	−0.28	2.36	.91	.53	**.21**	.01
Ethnicity, Hispanic	−3.14	2.89	.28	0.31	0.26	.23
Ethnicity, Asian	−2.34	2.6	.37	−0.07	0.23	.77
Ethnicity, other	4.38	4.57	.34	0.56	0.41	.17
Vocation or some college	**6.56**	3.31	**.05**	**−0.65**	**.30**	**.03**
College graduate	**7.93**	**3.40**	**.02**	−0.53	0.30	.08
Income < $45,000	−0.09	2.21	.97	−0.02	0.20	.94
Income > $75,000	−1.67	1.78	.35	0.22	0.16	.17
Employed	−0.67	1.78	.71	−0.01	0.16	.95
Married or partnered	−0.59	1.72	.73	**0.33**	**0.15**	**.03**
Time since diagnosis, years	−0.35	0.34	.30	0.002	0.03	.93
Mastectomy with reconstruction	0.07	1.78	.97	−0.19	0.16	.23
Mastectomy without reconstruction	1.38	1.78	.44	−0.01	0.16	.94
Chemotherapy ever	−1.22	2.09	.56	0.08	0.19	.65
Ever took tamoxifen	−2.52	2.79	.37	0.15	0.25	.54
Chemotherapy-tamoxifen interaction	4.27	3.28	.20	0.25	0.29	.39
Perimenopausal	−0.09	2.61	.97	−0.14	0.23	.55
Postmenopausal	−1.87	2.61	.46	−0.32	0.23	.16
Menopause transition	**−3.33**	**1.72**	**.05**	−0.02	0.16	.92
Number of medical conditions	**−2.93**	0.76	**.0001**	−0.11	0.07	.12
Emotional well-being	**0.18**	**0.05**	**.0001**	**0.06**	**0.0004**	**< .0001**
Physical functioning	**0.49**	**0.04**	**< .0001**	**0.01**	**0.003**	**.001**
Outlook: vulnerability	**−0.98**	**0.17**	**< .0001**	**−0.03**	**0.02**	**.03**

NOTE. The following parameters were measured: dependent variables, age, education indicators (comparison group: high school education or less), income indicators (comparison group: income $45,000 to $75,000), employment indicator (comparison group: not employed full or part time), ethnicity indicator (comparison group: white), married or partnered indicator (comparison group: unpartnered), time since diagnosis, mastectomy indicators (comparison group: lumpectomy), chemotherapy indicator (comparison group: did not receive chemotherapy), ever took tamoxifen indicator (comparison group: never took tamoxifen), tamoxifen or chemotherapy interaction indicator (comparison group: did not have both tamoxifen and chemotherapy), menopausal indicators (comparison group: premenopausal), menopause transition indicator (comparison group: did not change menopause status after treatment), number of medical conditions, emotional well-being as measured by the SF-36, physical functioning as measured by the SF-36, and vulnerability measured by the Outlook on Life scale. Figures in bold indicate statistically significant parameters in each model.

Abbreviation: SF, ???.

*P value from F test for significant overall regression.

†P value from *t* tests of individual parameter estimates.

observed prospectively for 1 year to determine the rate of amenorrhea in relationship to primary treatment.[12] We believe that the CAMS study sample described here is the first examination of a cohort of younger, long-term breast cancer survivors (mean of 6 years after diagnosis). In addition, the focus on the interface of reproductive health outcomes and QOL in the CAMS sample responds to a unique set of issues in this survivor population.

In this report, we have confirmed a substantial degree of psychologic distress in younger women after breast cancer that persists many years after the diagnosis. This is especially evident in the youngest women who were between 25 and 34 years of age at diagnosis, who reported significantly poorer emotional and social function and lower levels of energy than population norms from women without a breast cancer history. Although there is a gradient of emotional dysfunction from the youngest to the oldest women in this cohort (Table 4), there were no age-related differences in assessment of global QOL, or the meaning and vulnerability assessments. Better general health perceptions were positively associated with more than a high school education, better emotional and physical functioning, fewer comorbid conditions, and not having gone through the menopause transition as a result of therapy. Better ratings of QOL were significantly and positively associated with being African-American, being in a partnered relationship, and having better emotional and physical functioning. Perceptions of greater vulnerability were negatively associated with both outcomes, supporting the potent impact of vulnerability and fear of recurrence on health outcomes in breast cancer survivors.[48]

The findings from these models are also consistent with our prior research in a broader age range of breast cancer survivors,[10] in which the number of comorbid conditions and emotional and physical functioning predicted health perceptions, and being African-American and having better emotional functioning predicted better QOL. On the basis of other research, it is not surprising that the predictors in these two models are somewhat

different, given that other studies have shown that the general health perceptions scale more often is predicted by physical factors (eg, comorbid conditions or decreased physical abilities),[49] and that single-item QOL scales draw on both physical and emotional predictors (eg, emotional functioning and social support).[50] For this sample of younger women with breast cancer, it appears that specific treatments for breast cancer have had little direct influence on subsequent QOL, with the exception of the menopause transition, which is a result of adjuvant treatment.

The confirmation of these predictive models in this second independent sample of breast cancer survivors provides additional support for these observations. Emerging from this report, as well as in other research from our group,[51] is some evidence that African-American women may fare better after breast cancer than other ethnic groups. In our other research, we have found that African-American women report finding more meaning in life after breast cancer,[51] and this provides support for a possible mechanism by which these ethnic differences occur.

How do we reconcile the differences and similarities in QOL outcomes across diverse studies and age groups of breast cancer survivors? Consistent with the broader literature on QOL outcomes in younger women with breast cancer, the emotional impact of the disease is substantial, and most evident in the youngest women. Younger women are at a time in life when a serious disease like cancer is not anticipated and is disruptive. In addition, the impact of treatment on reproductive health may contribute to changes in emotional well-being. Indeed, our results suggest that treatment-related menopause was particularly problematic for the youngest women and was associated with poorer emotional functioning. Women who are older at diagnosis (eg, the oldest women in this cohort) may have greater emotional resiliency from prior life experiences that are brought to bear when facing a cancer diagnosis. However, older women may have less physical resiliency in the face of breast cancer treatments because of underlying comorbid conditions or increasing physical limitations associated with age.[9,10] The divergence between physical and emotional functioning in relationship to age is generally observed in healthy populations (SF-36 norms[20]), and the age-related differences in the impact of breast cancer diagnosis and treatment on emotional and physical functioning may represent an exaggeration of these normative findings.

There are several important limitations of this study. First, although we attempted to recruit as representative a sample as possible of younger breast cancer survivors, many women were not accessible or declined to participate in the study. This was especially true among some ethnic minority women and women from the community hospital.[13] It is challenging to identify cancer survivors who might participate in research studies, yet cancer registries provide us with one of the best sources.[13] It is possible that the women who responded to the study invitation were more resilient and higher functioning, and therefore, we may be underestimating the impact of breast cancer in younger women. In addition, as with any survey study, there may be inaccuracies in self-report of information on health history, reproductive health, emotional concerns, or other topics that we queried. Finally, these younger breast cancer survivors were recruited from one large urban area, and their experiences may not represent those of all younger women with breast cancer.

Despite these limitations, we believe that this report describes one of the largest and most diverse cohorts of younger breast cancer survivors in the literature to date. Our findings provide important insights into the late effects of this disease in younger women. Despite its known effect on reproductive health, systemic adjuvant therapy did not appear to have negatively influenced either physical or emotional functioning in these younger women, and instead, women who either did not choose or were not advised to have adjuvant therapy fared somewhat worse emotionally. However, it is clear that loss of reproductive function (early menopause), the ability to have children, and many specific symptoms are associated with breast cancer treatments. The descriptive findings in this report may be useful to clinicians and patients, and it is important for us to acknowledge that many symptoms and problems persist long beyond the acute phase of breast cancer treatment.

AQ: N

ACKNOWLEDGMENT

We are grateful for the excellent support provided by Amber Pakilit and Laura Abraham, who were the research assistants for this study. In addition, we express our great appreciation to the women who participated in this study.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.

REFERENCES

1. Surveillance, Epidemiology, and End Results (SEER) Program SEER*Stat Database: Incidence—SEER 9 Regs Public Use, Nov 2002 Sub (1973 to 2000), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2003, based on the November 2002 submission, 2003. http://www.seer.cancer.gov

2. Chu KC, Tarone RE, Kessler LG, et al: Recent trends in U.S. breast cancer incidence, survival, and mortality rates. J Natl Cancer Inst 88:1571-1579, 1996

3. Wenzel LB, Fairclough DL, Brady MJ, et al: Age-related differences in the quality of life of breast carcinoma patients after treatment. Cancer 86:1768-1774, 1999

4. Bloom JR, Kessler L: Risk and timing of counseling and support interventions for younger women with breast cancer. J Natl Cancer Inst Monogr 199-206, 1994

AQ: O

5. Bloom JR, Stewart SL, Johnston M, et al: Intrusiveness of illness and quality of life in young women with breast cancer. Psychooncology 7:89-100, 1998

6. Dow KH, Lafferty P: Quality of life, survivorship, and psychosocial adjustment of young women with breast cancer after breast-conserving surgery and radiation therapy. Oncol Nurs Forum 27:1555-1564, 2000

7. Schag CA, Ganz PA, Polinsky ML, et al: Characteristics of women at risk for psychosocial distress in the year after breast cancer. J Clin Oncol 11:783-793, 1993

8. Ganz PA, Hirji K, Sim MS, et al: Predicting psychosocial risk in patients with breast cancer. Med Care 31:419-431, 1993

AQ: P

9. Ganz PA, Rowland JH, Desmond K, et al: Life after breast cancer: Understanding women's health-related quality of life and sexual functioning. J Clin Oncol 16:501-514, 1998

10. Ganz PA, Desmond KA, Leedham B, et al: Quality of life in long-term, disease-free survivors of breast cancer: A follow-up study. J Natl Cancer Inst 94:39-49, 2002

11. Bines J, Oleske DM, Cobleigh MA: Ovarian function in premenopausal women treated with adjuvant chemotherapy for breast cancer. J Clin Oncol 14:1718-1729, 1996

12. Goodwin PJ, Ennis M, Pritchard KI, et al: Risk of menopause during the first year after breast cancer diagnosis. J Clin Oncol 17:2365-2370, 1999

13. Pakilit AT, Kahn BA, Petersen L, et al: Making effective use of tumor registries for cancer survivorship research. Cancer 92:1305-1314, 2001

14. Bickell NA, Chassin MR: Determining the quality of breast cancer care: Do tumor registries measure up? Ann Intern Med 132:705-710, 2000

15. Malin JL, Kahn KL, Adams J, et al: Validity of cancer registry data for measuring the quality of breast cancer care. J Natl Cancer Inst 94:835-844, 2002

16. Ganz PA, Day R, Ware JE Jr, et al: Baseline quality-of-life assessment in the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial. J Natl Cancer Inst 87:1372-1382, 1995

17. Day R, Ganz PA, Costantino JP, et al: Health-related quality of life and tamoxifen in breast cancer prevention: A report from the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Clin Oncol 17:2659-2669, 1999

18. Ganz PA, Rowland JH, Meyerowitz BE, et al: Impact of different adjuvant therapy strategies on quality of life in breast cancer survivors. Recent Results Cancer Res 152:396-411, 1998

19. Sowers MF, Crawford S, Sternfeld B, et al. SWAN: A multicenter, multiethnic, community-based cohort study of women and the menopausal transition, in Lobo R, Marcus R, Kelsey J (eds): Menopause. New York, NY, AQ: Q Academic Press, 2000, pp 175-188

20. Ware JE Jr: SF-36 Health Survey: Manual and Interpretation Guide. AQ: R Boston, MA, The Health Institute, New England Medical Center, 1993

21. Hays RD, Sherbourne CD, Mazel RM: The RAND 36-Item Health AQ: S Survey 1.0. Health Econ 2:217-227, 1993

22. Cantril H: The Pattern of Human Concerns. New Brunswick, NJ, AQ: T Rutgers University Press, 1965

23. McHorney CA, Kosinski M, Ware JE Jr: Comparisons of the costs and quality of norms for the SF-36 health survey collected by mail versus telephone interview: Results from a national survey. Med Care 32:551-567, 1994

24. Ware JE Jr, Kosinki M, Keller SD: SF-36 Physical and Mental Health AQ: U Summary Scales: A User's Manual. Boston, MA, The Health Institute, 1994

25. McDowell I, Newell C: Measuring Health, A Guide to Rating Scales AQ: V and Questionnaires (ed 2). New York, NY, Oxford University Press, 1996

26. Radloff LS: The CES-D Scale: A self-report depression scale for AQ: W research in the general population. Appl Psychol Measure 1:385-401, 1977

27. Greendale GA, Hogan P, Shumaker S: Post Menopausal Estrogen/Progestins Intervention Trial (PEPI) Investigators: Sexual functioning in post menopausal women—The Post Menopausal Estrogen/Progestins Intervention (PEPI) Trial. J Womens Health 5:445-458, 1996 AQ: X

28. Myers JK, Weissman MM: Use of a self-report symptom scale to detect depression in a community sample. Am J Psychiatry 137:1081-1084, 1980

29. Roberts RE, Vernon SW: The Center for Epidemiologic Studies Depression Scale: Its use in a community sample. Am J Psychiatry 140:41-46, 1983

30. Watson D, Clark LA, Tellegen A: Development and validation of brief measures of positive and negative affect: The PANAS scales. J Pers Soc Psychol 54:1063-1070, 1988

31. Thirlaway K, Fallowfield L, Cuzick J: The Sexual Activity Questionnaire: A measure of women's sexual functioning. Qual Life Res 5:81-90, 1996 [erratum in Qual Life Res 6:606, 1997]

32. Fallowfield L, Fleissig A, Edwards R, et al: Tamoxifen for the prevention of breast cancer: Psychosocial impact on women participating in two randomized controlled trials. J Clin Oncol 19:1885-1892, 2001

33. Ganz PA, Lee JJ, Sim MS, et al: Exploring the influence of multiple variables on the relationship of age to quality of life in women with breast cancer. J Clin Epidemiol 45:473-485, 1992

34. Bower JE, Ganz PA, Desmond KA, et al: Fatigue in breast cancer survivors: Occurrence, correlates, and impact on quality of life. J Clin Oncol 18:743-753, 2000

35. Meyerowitz BE, Desmond KA, Rowland JH, et al: Sexuality following breast cancer. J Sex Marital Ther 25:237-250, 1999

36. Arora NK, Gustafson DH, Hawkins RP, et al: Impact of surgery and chemotherapy on the quality of life of younger women with breast carcinoma: A prospective study. Cancer 92:1288-1298, 2001

37. Cimprich B, Ronis DL, Martinez-Ramos G: Age at diagnosis and quality of life in breast cancer survivors. Cancer Pract 10:85-93, 2002

38. Anonymous: Breast cancer in younger women. J Natl Cancer Inst Monogr, 1994 AQ: Y

39. Shapiro CL, Recht A: Late effects of adjuvant therapy for breast cancer. J Natl Cancer Inst Monogr 101-112, 1994 AQ: Z

40. Reichman BS, Green KB: Breast cancer in young women: Effect of chemotherapy on ovarian function, fertility, and birth defects. J Natl Cancer Inst Monogr 125-129, 1994 AQ: AA

41. Dow KH, Harris JR, Roy C: Pregnancy after breast-conserving surgery and radiation therapy for breast cancer. J Natl Cancer Inst Monogr 131-137, 1994 AQ: BB

42. Theriault RL, Sellin RV: Estrogen-replacement therapy in younger women with breast cancer. J Natl Cancer Inst Monogr 149-152, 1994 AQ: CC

43. Schover LR: Sexuality and body image in younger women with breast cancer. J Natl Cancer Inst Monogr 177-182, 1994 AQ: DD

44. Northouse LL: Breast cancer in younger women: Effects on interpersonal and family relations. J Natl Cancer Inst Monogr 183-190, 1994 AQ: EE

45. Mor V, Malin M, Allen S: Age differences in the psychosocial problems encountered by breast cancer patients. J Natl Cancer Inst Monogr 191-197, 1994 AQ: FF

46. Bloom JR, Stewart SL, Johnston M, et al: Sources of support and the physical and mental well-being of young women with breast cancer. Soc Sci Med 53:1513-1524, 2001

47. Allen SM, Shah AC, Nezu AM, et al: A problem-solving approach to stress reduction among younger women with breast carcinoma: A randomized controlled trial. Cancer 94:3089-3100, 2002

48. Bower JE, Meyerowitz BE, Desmond KA, et al: Perceptions of meaning and vulnerability following breast cancer. Presented at Am Psychol Assoc Annu Meeting, San Francisco, CA, 2001 AQ: GG

49. Krause NM, Jay GM: What do global self-rated health items measure? Med Care 32:930-942, 1994

50. Schag CA, Heinrich RL, Aadland RL, et al: Assessing problems of cancer patients: Psychometric properties of the cancer inventory of problem situations. Health Psychol 9:83-102, 1990

51. Giedzinska AS, Meyerowitz BE, Ganz PA, et al: Health-related quality of life in a multiethnic sample of breast cancer survivors. Ann Behav Med (in press) AQ: HH